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Determination of preferred conformations of ibuprofen in chloroform by 2D NOE spectroscopy

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ABSTRACT

Solution of an anti-inflammatory drug ibuprofen ((RS)-2-(4-isobutylphenyl) propionic acid) in chloroform was studied by nuclear magnetic resonance spectroscopy. A set of 2D NOESY spectra was analyzed in order to obtain atom–atom distances. Since ibuprofen is known to exist as an ensemble of different conformations, these distances are averaged over the ensemble. To compare experimental and calculated distances, three models of averaging were concerned. Our data allowed to determine the dominant conformers of ibuprofen dissolved in chloroform. The population of conformers in the saturated solution leads to a certain crystal morphology formed within the nucleation process. Observed and calculated ^{13}C chemical shifts (at the DFT/B3LYP/6-311+G(2d,p) level) were in good agreement.

1. Introduction

Information on properties of conformations of biologically active molecules, including nonsteroidal anti-inflammatory drugs, is of paramount importance for better understanding of the structure–activity relationships underlying their biological effect and of the mechanism of their action on an organism (Llorens et al., 2002; Marot et al., 2000; Selinsky et al., 2001). Experimental determination of spatial structure and conformational state of biologically active molecules attracts an increasing interest (Butts et al., 2012; Efimov et al., 2013; Fernandes et al., 2003; Khodov et al., 2013).

Ibuprofen ((RS)-2-(4-isobutylphenyl) propionic acid, $C_{13}H_{18}O_2$) is a nonsteroidal anti-inflammatory drug used in treating rheumatoid arthritis, osteoarthritis, and other diseases for pain relief and alleviation of fever (Adams et al., 1967). It was firstly synthesized by Adams with his colleagues in 1961 and called BTS 13621. It has an outstanding biological activity among substituted phenylalkane and alkene acids (Adams, 1992; Adams et al., 1967).

The ibuprofen molecule can be regarded as a benzene ring having two para-substituents (Fig. 1). One of them is the $–CH_2–CH–(CH_3)_2$ chain, and the other contains a carboxyl group ($–CH(CH_3)COOH$). Ibuprofen molecules possess a chiral centre at the α-carbon atoms (C6 in Fig. 1) and can exist as R(−) and S(+) enantiomers. Commercially available ibuprofen is also a racemic mixture of both enantiomers. Geisslinger et al. have shown that only the S(+) form is pharmaceutically active (Geisslinger et al., 1989). The inactive R(−) ibuprofen, however, may undergo a unidirectional chiral inversion into the active S(+) form in vivo (Geisslinger et al., 1989; Lin et al., 2004).

Ibuprofen molecule is flexible due to internal rotations of the propionic acid fragment and the isobutyl group. Namely, it is determined by varying four dihedral angles around the C1–C6, C6–C3, C2–C7, and C7–C8 bonds: $\tau 1$ (O–C1–C6–C3), $\tau 2$ (C1–C6–C3–C4), $\tau 3$ (C5–C2–C7–C8), and $\tau 4$ (C2–C7–C8–C9), respectively. If the ibuprofen molecule is regarded as a para-substituted aromatic ring, its different forms can be described in terms of relative orientations of the substituents (below or above the ring plane). The rotations around the C6–C3 and C2–C7 bonds are not correlated, which is evidenced by comparing conformers pairwise (see Table 1). Variety of conformations results in variety of geometric and electronic properties of molecules in solution.

Eight possible different conformations of ibuprofen were found in Vueba et al. (2008) based on quantum chemical calculations. Having compared the results of vibrational spectroscopy and quantum chemical calculations, the authors suggest that a limited number of conformers can be considered due to a very small energy difference in pairs between the A and B, C and D, E and F, and G

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